polycystic kidneys. The phthalein test, however, showed no evidence of renal insufficiency.

These two findings in polycystic kidneys tally with the clinical picture in this disease, renal function being apparently adequate for years until some intercurrent infection causes impairment, and eventually uremia and death.

Rowntree's case of polycystic kidney is an example of good elimination before, and ours of faulty elimination after, the intercurrent infection.

This brief report is presented for the purpose of calling attention to certain interesting phases of phthalein elimination, and with no intention of minimizing the importance of the test, which, on the contrary, we believe to be of the greatest value for the determination of renal efficiency.

PRIMARY ADENOMATA OF THE LIVER SIMULATING HANOT'S HYPERTROPHIC LIVER CIRRHOSIS.

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Adenomata of the liver are rare, and only the most meager mention of these tumors can be found in our recent text-books or systems of medicine, or even in our standard works on pathology. From the literature we have been able to collect but 44 cases of this condition, 16 of which were solitary, and 28 multiple. Of the latter 28 there were 21 associated with the atrophic cirrhosis of Laennec and the remaining 7 had no mention of any cirrhosis whatever. These primary cases were accidental discoveries at autopsy, and no reference was made to any symptoms which they may have induced. In 25 of the 44 cases the tumors were composed of modified liver parenchyma, and in 19 the structure was that of agglomerations of large bile ducts. Of these 19 there were 4 multiple and 15 solitary.

The greater portion of these cases were unaccompanied by any sort of clinical history, and were apparently collated for the sole purpose of the statistics of incidence.

In his book *Diseases of the Liver*, Rolleston devotes some space to the consideration of adenoma of this organ. He divides all adenomata into three classes: (1) Composed of or derived from the ordinary parenchymal cells; (2) those derived from the bile ducts; (3) those due to the inclusions of adrenal "rests." Since the case herewith reported comes under the first class we will confine our attention to it alone.

In common with all who refer to the condition at all, Rolleston holds that the majority of instances of multiple liver adenomata are associated with and secondary to cirrhosis of that organ, the condition being essentially a compensatory process of cell hypertrophy to offset the destruction of the parenchyma by the disease. He regards them as "exaggerations of the hobnails seen in portal cirrhosis," and states that they are to be explained as a final stage of this nodular hyperplasia. Necrosis, fatty metamorphosis, and portal thrombosis are particularly apt to follow. On the other hand, Engelhardt ascribes their etiology to a toxin which has been producing the connective-tissue hyperplasia of the cirrhosis and is supported later in this view by Dieulafoy. The toxins of malaria have been known to produce adenoma of the liver, and injections of toxins resulting from blastomycetic infections have produced the same result. In favor of the compensation theory, it may be mentioned that in the portal cirrhoses where the cell destruction is most marked the majority of instances of adenoma occur, while in the types of cirrhosis which are characterized by long preservation of the liver cells it never occurs.

A very common fate of adenoma of the liver is their malignant transformation into carcinomata, according to Sabourin, who has written extensively on this phase of the subject. This is usually fairly early in the history of the adenomatous condition, and is nearly always accompanied by infiltration of the portal vessels, with consequent tumor-cell emboli, by spread to the other surrounding structures, and by metastasis to various tissues by way of the lymphatics.

According to Rolleston and emphasized by Engelhardt, in nearly all of the cases of multiple adenomata there is associated with the cirrhosis a thrombosis of the portal vein, and consequently a high percentage of these tumors are marked by the vomiting of blood and by ascites.

Many of the foregoing data are of interest in the light of the case here reported, and are, therefore, selected for mention.

Case History.—The patient, C. M. H., aged thirty-one years; married; occupation, paper-box manufacturer. First consulted one of us on May 31, 1906, complaining of weakness, loss of appetite, pain, dragging in the abdomen, and jaundice.

He has had all the infections of childhood, since which time he has been in perfect health until about two years ago, when he developed what was then diagnosticated as a severe attack of influenza. He dates his present illness from that attack, never having been well since. He denies all venereal disease. He has never been in the tropics, and has never suffered from malaria or dysentery. His habits are of the best. He uses no tobacco or alcoholic stimulants. He complains of weakness, dragging, and fulness of the abdomen, dull pain in the back and loins, and loss of appetite. He states that he has had several attacks of feverishness for which he could not account. He has never bled from the gums, nose, stomach, or rectum. He never suffers from headache, and his bowels are regular. The stools, he states, are light yellow in color, and he has never observed them clay colored. His urine is abundant, dark in color, and deposits much brick-dust sediment. He has noticed that the jaundice from which he suffers fluctuates in intensity. Sometimes his skin is extremely dark and at other times much bleached.

EXAMINATION. The patient is a well-built man, his muscles are flabby, and the visible mucous surfaces are pale. His skin and conjunctivæ are universally and deeply bile-stained. There is no edema or cyanosis. His respirations are quiet and the pulse slow. The skin is dry and a little harsh.

Lungs: Apart from a moderate degree of emphysema they seem normal.

Heart and Arteries: The cardiac impulse is visible in the fifth interspace 8 cm. to the left of the midsternum. No friction or thrill over the precordium exists. The cardiac dulness is nearly effaced by a hyper-resonant note. There is a soft basic systolic murmur slightly conducted into the carotids and also heard over the pulmonic and aortic interspaces. A soft systolic apical murmur is heard, conducted feebly to the left. The pulse is 60, regular, soft, and easily compressed. The systolic blood pressure is 130 mm. of mercury; the diastolic pressure, 80 mm.

Blood: Red cells, 3,250,000; white cells, 8000; hemoglobin, 70 per cent.; color index, 1. The red cells presented no nucleated forms and no poikilocytosis. No malarial parasites seen. The staining reaction was good.

Abdomen: The whole upper half of the abdomen is full and prominent. There is a slight right inguinal hernia, easily reducible. There are no enlarged veins traversing the abdomen or chest; no dulness exists in either loin or in the dependent parts of the abdomen when standing. The kidneys are not palpable.

Liver: The dulness of the right lobe of the liver in the midclavicular line extends downward from the level of the fifth rib 18 cm., while that of the left lobe extends downward from the sternoxiphoid articulation 20 cm. The liver border is rounded, firm in consistency, painless on pressure, and has no palpable nodules. A deep notch, easily palpable, separates the large and heavy left lobe from the right. Another deep notch exists in the position of the fissure of the gall-bladder. The latter organ, however, is not palpable.

Spleen: The dulness of the spleen extends from the seventh rib downward and forward, whence it apparently blends with the dulness of the left lobe of the liver. Its lower border is firm and smooth.

Rectum: Examination of the rectum showed no hemorrhoids. The prostate gland was normal in size and consistency and perfectly smooth.

Glands: No enlarged lymph glands were detectable. There was no joint or bone tenderness.

Nervous System: Examination of the nervous system was entirely negative. The ophthalmoscope showed no changes in the optic disks or retinæ.

Urine: Twenty-four-hour specimen; amount, 3 pints. Reaction, acid; color, dark amber; specific gravity, 1022; foam, bile-stained. All tests for bile, positive. No albumin or sugar; no indican. There are a few bile-stained casts. No blood cells discernible. Amorphous urates in abundance.

The stool was light yellow in color and soft in consistency. It contained no mucus, amebæ, blood, or other pathogenic parasites.

He was again examined in April, 1907, and the following notes taken:

Jaundice much more intense. Slight soft edema about the tibiæ, no cyanosis, slight general emaciation. The left lobe of the liver almost fills the upper half of the abdomen, extending downward two fingers' breadth below the umbilicus. The right lobe, though very large, appears much like an appendage to the left. The spleen, owing to the large left lobe of the liver, is palpated with difficulty. No enlarged veins are visible and no signs of free fluid exist in the peritoneal cavity. No hemorrhoids are present. Systolic, basic, and apical murmurs are present. The systolic blood pressure is 120 mm. of mercury. The blood picture is that of a secondary anemia. The stools are light though not clay colored. The patient states that the stools change their color from time to time. Physically, he is much weaker, has a fickle appetite, and suffers from great itching of the skin and from insomnia.

He was observed from time to time during the year 1907, but no remarkable change in his condition was found. His jaundice would fluctuate; at times he would become dark and again much lighter. His stools, while not clay-colored, were much lighter than when he first came under observation. He resided in the country and remained in fair health until the fall of 1908, when all his symptoms became much worse: his jaundice was intense, his stools about clay-colored, his urine scanty and full of bile, his gums vascular and bleeding on the slightest provocation, but without hemorrhage from any other mucous surface. His liver remained about as described above, the left lobe always being the most prominent. There was no evidence of portal obstruction. A week before his death, however, changeable dulness was detected in each flank, but not enough fluid existed to produce a fluctuation wave. A few days prior to death he became delirious, drowsy, gradually passed into deep coma, which lasted about forty-eight hours, and died.

The complex of symptoms presented during the course of the disease were: (1) A long, continuous jaundice fluctuating in intensity; (2) a gradual but progressive liver enlargement until it became of enormous size, with special prominence of the left lobe; (3) definite though moderate enlargement of the spleen; (4) absence of acholic stools until within a few days of death; (5) absence of ascites, hemorrhages from mucous surfaces, or enlargement of the abdominal or hemorrhoidal veins; (6) presence of attacks of abdominal pain, with febrile reaction; (7) abundant bile-stained urine; (8) cholemia and death.

The presence of the above complex naturally led to a diagnosis of hypertrophic biliary cirrhosis of the type of Hanot. Owing to a moderately well-developed panniculus, and also to the fact that most of the tumor masses located on the ventral wall were small, the nodules were not palpable.

AUTOPSY. Mr. C. M. H. Performed by Dr. H. W. Carey, March 8, 1908. Autopsy No. 105, from the Samaritan Hospital records.

The body is that of a well-nourished man, 170 cm. in length. There is marked jaundice of universal distribution, together with much staining of the conjunctivæ. The pupils are equal. The abdomen is slightly distended and full in the flanks. There is slight edema of both ankles. Rigor mortis is well marked. There are no enlargements of the superficial lymph glands. The superficial veins are not enlarged. The body has been embalmed.

The peritoneal surfaces are normal save for a line of adhesions along the course of the urachus to the coils of the intestines above the pubes. It contains no dilated veins. The appendix is normal. The coils of intestines are normal.

On raising the costal flap no enlargement of the internal mammary veins is noted.

The lungs are normal except for two small infarcts on the lower border of the right lower lobe. There is slight edema and congestion of the lower lobes of both.

The bronchial glands are normal.

The pericardial sac is normal.

The heart shows considerable thickening of the aortic valve, due to vegetations on the proximal side of the leaflets, which narrows the valvular orifice and renders the valve as a whole, incompetent.

The spleen is about normal in size and weighs 645 grams. It is negative throughout. Nearby in the omentum are two small accessory spleens about 1 cm. in diameter, but presenting nothing unusual in their structure.

The stomach is normal.

The pancreas is normal.

The kidneys are normal save for a marked pallor and indistinct markings in the right.

The adrenals are normal. There are no signs of tumor growth seen.

The intestines, bladder, genitalia, and bone-marrow are normal.

The liver: On opening the abdomen the lower border of the liver presents in the midline 11 cm. below the tip of the ensiform cartilage. On removing the chest wall the portion first visible is seen to be the left lobe, the right lobe being pushed well into the right flank and encroaching above upon the right pleural cavity. On removal of the liver it is found to weigh 2445 grams (5.3 pounds).

In color, the liver is nearly all of a peculiar yellowish green, but a small portion is fairly normal purplish red. The whole surface is broken up into literally innumerable nodules, leaving no part of the surface smooth. Over the upper surface these are approximately 1 mm. to 1 cm. in diameter, while on the under surface most of them are much larger, measuring from 2 cm. to 3 cm. These nodules, where not bile-stained, are dark purplish red and do not show the light yellowish or bleached appearance common to fatty deposits in nodular livers. The interstices between the nodules are not rich in fibrous tissue nor are the depressions so sharp as in the surfaces of atrophic cirrhosis. In some places the capsule is thickened, but for the most part it is surprisingly thin considering the evident abnormality. On section the entire liver is found to be divided into thousands of small round masses of sizes varying about as the nodules upon the surface. Nothing approaching the appearance of normal liver tissue is identifiable to the naked eye. The consistence of these masses is firm but by no means hard. The liver as a whole, is somewhat firmer than normal but has not that absolute leathery feeling common to advanced cirrhosis. The cut surface of the nodules seems somewhat paler than the nodules appear on the outer surface, whether they are bile stained or not. Each mass seems to be surrounded by a fine connective-tissue capsule.

The gall-bladder wall is much thickened, but the mucosa, though pale, is normal in appearance.

The portal veins are clear throughout. No thrombi or other obstructions and no dilatations are found in them or their tributaries.

Microscopic Description. The lungs are normal except for the presence of the infarcts and slight congestion and edema.

The heart muscle is normal.

The spleen shows a slight chronic interstitial splenitis. The two small accessory organs have a normal splenic structure.

The kidneys: The right shows slight hemorrhage. The left is normal.

The mesenteric lymph nodes, stomach, and intestines are normal.

The liver: The blocks of tissue studied were fixed in formalin. The paraffin, celloidin, and freezing methods were used. The sections were stained in hematoxylin-eosin, eosin-methylene blue, Mallory's connective-tissue stain, v. Gieson's stain, safranin, phosphotungstic acid hematoxylin, and scharlach R.

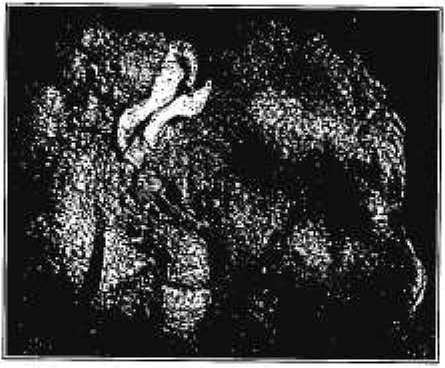

FIG. 1.—Adenoma of the liver, showing under surface. Note large size of the nodules and the great enlargement of the left lobe.

As the sections from the different portions of the liver are gradually gone over, the first point which impresses one is the almost total absence of normal or even relatively normal parenchyma. In its stead one sees a picture composed of generally round masses of cells of different sizes, each surrounded by a definite capsule. At first one is inclined to believe each mass derived from an original lobule of the liver, but on closer inspection, this structure is nowhere definitely preserved. Sometimes one sees what appears to be the remnant of a central vein but in most cases even this is absent. An occasional portal space has survived the change sufficiently to be recognizable. The arrangement of the cells corresponds in places to that of the normal parenchyma, but the likeness is limited, however, to the fact that the cells form minute bile-ducts, and seem to be disposed about a lumen which in some instances is apparently filled with a cast composed of closely

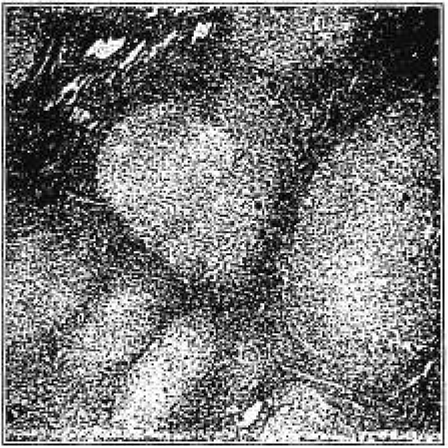

FIG. 2.—Adenoma of the liver (× 70). Single encapsulated nodules. At lower left corner are parts of four lobules coalescing to form a new adenoma nodule.

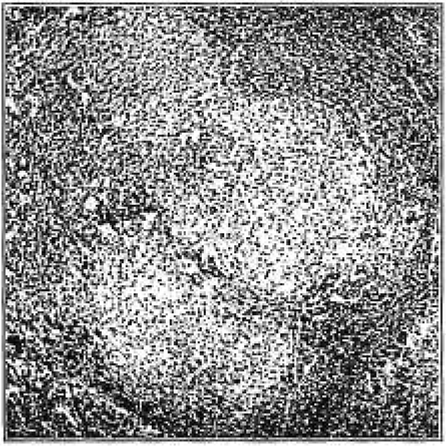

FIG. 3.—Adenoma of the liver (× 200). Same location as in Fig. 2. Cells brought out more clearly.

packed masses of pigment granules and detritus. In the majority of cases the cell masses are mere groups with no definite arrangement like that of the liver cells. They are noticeably poorly supplied with bloodvessels for the most part. Some, however, have quite a number of small twigs running along between the duct-like strands of cells (Fig. 4). In all instances they arise from the capsular vessels.

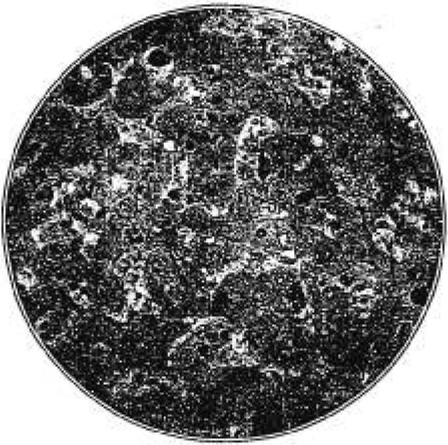

FIG. 4.—Adenoma of the liver (× 800), showing details of the cells and their likeness to the normal cells of the liver. Note the double nucleation of some of the cells and the pigment casts of the ducts.

The cells are polygonal in shape, but not as sharply polygonal as are the normal cells. These tend to be rather more rounded and irregular. No columnar cells are seen, neither are there any reversions to embryonic type. The characteristic cell is much larger than that of the liver cell, and may be three or four times its size. Usually their size is definite for a certain mass, one mass containing only large ones, while another is made up of much smaller cells. The size of the cells is generally much greater than usual in sections taken from the deeper portions of the organ and coincidentally the deposit of pigment in the cells and between them, which is widely distributed, is much more prominent in these deeper portions. The pigmentation is in the form of granules of coarse and finer sizes which often packs the cells to such an extent that their morphology is totally obscured. It is partly hematogenous and partly biliary in origin, the hematogenous granules coming out clearly by the ferrocyanide-HCl test in frozen sections.

The cells when not obscured by pigment show a clear, homogeneous protoplasm, and with some stains, particularly v. Gieson's, the cell body takes on an almost glairy appearance. The protoplasm takes a light pink stain with eosin-methylene blue and a slightly darker hue with hematoxylin-eosin. In the sections stained by v. Gieson's stain there is marked variation of the protoplasmic stain, those cells in what seems the older portions taking the lightest coloring and some having totally lost their staining capacity. The cells rest on a delicate basement membrane, which stains clearest in the phosphotungstic acid hematoxylin preparations. No intercellular bridges of any kind are seen.

The nuclei are uniform in size, irrespective of the size of the cells. They take a pale blue stain in the eosin-methylene blue preparations and show no marked chromatin network. A good number of cells are doubly nucleated, and in these the daughter nuclei are darker than the others, and have a more decided chromatin network. Wherever it can be determined, these nuclei have always divided by simple fission. The very few examples of karyokinesis observed in the safranin-stained sections do not show any remarkable characteristics.

The masses of cells are surrounded by strands of connective tissue of moderate thickness and density. Near the junction of several of these cell groups the areas of connective tissue are of considerable extent, and, indeed, throughout the sections the amount of connective tissue and its arrangement at first suggest cirrhosis. With closer study some facts appear which seem in our judgment to controvert this idea. In the first place the lobule of the liver as such is not the histological unit giving rise to these growths. In the multilobular or Laennec's type of cirrhosis we see small groups of lobules surrounded by bands of connective tissue, the latter conforming more or less closely to the outlines of the lobules in the group; nevertheless we never see the connective tissue splitting up several lobules, including half the resulting divisions in a single group and entirely leaving out the other portions. In this case, however, there appears to be a somewhat analogous process going on. There are certain areas where the adenomatous transformation is not complete. In these instances there is apparently a centre of transformation in one portion of a lobule from which the adenomatous change gradually spreads, slowly involving parts of neighboring lobules. The capsule forming about this newly evolved growth creeps around the adenomatous portions and merges them into one mass, the other and normal portions remaining outside the capsular wall.

Again, of the two processes, cellular growth and connective-tissue proliferation, the latter seems relatively much younger and is certainly much younger than a like amount of cirrhotic connective tissue. Only in the deeper and older portions of the growth is there any density and tendency to hyalinization, and in contradistinction to this the cells in these locations show disintegrating nuclei, poorly and unevenly stained protoplasm, which is often hyaline, and even large areas that have undergone degeneration and become necrotic. Nor do we see the bile-duct formation to anything like the extent seen in nearly all cases of cirrhosis approaching this grade of connective-tissue formation. In places one sees areas of relatively normal but greatly compressed liver cells. That these are groups composed of many lobules can be easily seen, and here it is noteworthy that the connective-tissue growth is entirely absent, the compression being the result of the pressure of the surrounding cell masses and their capsules.

Nowhere in the sections do we see any intercellular or intralobular connective-tissue invasion except to the slightest extent. Such invasion as can be seen is brought out only by the special connective-tissue stains.

There are several areas, as above mentioned, where it is possible to see a direct change in the parenchyma from the normal to the adenomatous type. It is significant that the connective-tissue capsules surrounding them are rudimentary in comparison to the capsules of the older growths. In these newer portions the connective-tissue cells are younger and more nearly of the fibroblastic type, and there is no hyaline change visible. The amount of the fibrous proliferation seems proportional to the completeness of the transformation to the adenoma structure.

In the larger areas of connective-tissue formation one sees many large and small bile-ducts which in most cases are dilated. They are lined by cuboidal epithelium, and in many instances are filled with great masses of granular pigment of biliary origin.

No tendency to malignant transformation is anywhere noted. No new growth of any kind is seen anywhere else in the body.

We have here, then, a case of adenoma of the liver whose multiple nodules have replaced the liver substance to such an extent that only microscopically can any normal liver tissue be found. They are derived from the liver parenchyma itself, instances being seen of transformation in progress. Each tumor nodule is encapsulated. That this connective tissue is not the manifestation of a cirrhosis is demonstrated by: (1) Individual nodules do not spring from original individual lobules; (2) parts of many lobules are united in some instances to form the tumor nodules; (3) where the neoplasmic transformation is in progress we find these parts surrounded by only rudimentary capsules; (4) the few areas of normal though compressed liver tissue visible are not invaded by a connective-tissue overgrowth such as one would expect if the condition were one of cirrhosis; (5) there is no fatty metamorphosis, malignant transformation, other tumor formation or any abnormality of the portal veins.

The case herewith reported is of interest because (1) it presented the symptom complex of Hanot's hypertrophic biliary cirrhosis; (2) because the study of the liver does not bear out the generally accepted view that multiple adenomata are always secondary to and in compensation for liver cirrhosis; (3) because it shows the importance of recognizing the fact that symptoms identical with those produced by either the atrophic or the hypertrophic form of cirrhosis may take their origin from multiple adenomata.

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